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Chapter 4

Regulating Pharmaceutical Drugs—Health Canada

Office of the Auditor General of Canada

The Fall 2011 Report of the Auditor General of Canada comprises Matters of Special Importance, Main Points—Chapters 1 to 5, Appendices, and five chapters. The main table of contents for the Report is found at the end of this publication.

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For copies of the Report or other Office of the Auditor General publications, contact

Office of the Auditor General of Canada
240 Sparks Street, Stop 1047D
Ottawa, Ontario
K1A 0G6

Telephone: 613-952-0213, ext. 5000, or 1-888-761-5953
Fax: 613-943-5485
Hearing impaired only TTY: 613-954-8042
Email: distribution@oag-bvg.gc.ca

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Chapter

4

Regulating Pharmaceutical Drugs—Health Canada

Performance audit reports

This report presents the results of a performance audit conducted by the Office of the Auditor General of Canada under the authority of the *Auditor General Act*.

A performance audit is an independent, objective, and systematic assessment of how well government is managing its activities, responsibilities, and resources. Audit topics are selected based on their significance. While the Office may comment on policy implementation in a performance audit, it does not comment on the merits of a policy.

Performance audits are planned, performed, and reported in accordance with professional auditing standards and Office policies. They are conducted by qualified auditors who

- establish audit objectives and criteria for the assessment of performance;
- gather the evidence necessary to assess performance against the criteria;
- report both positive and negative findings;
- conclude against the established audit objectives; and
- make recommendations for improvement when there are significant differences between criteria and assessed performance.

Performance audits contribute to a public service that is ethical and effective and a government that is accountable to Parliament and Canadians.

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Regulating Pharmaceutical Drugs—Health Canada

Main Points

What we examined

Pharmaceutical drugs are mostly synthetic products made from chemicals. They are meant to improve the health and well-being of patients by helping to prevent and treat disease, reduce pain and suffering, and extend and save lives. Some higher-risk drugs, such as those used to treat diseases, require a prescription from a physician. Other lower-risk drugs, such as cough syrup and antacids, are sold without a prescription and are readily available to the public.

Health Canada, through the *Food and Drugs Act*, regulates the safety, efficacy, and quality of all pharmaceutical drugs for use by humans in Canada before and after the products enter the Canadian marketplace. The Department does this through a combination of scientific review, monitoring, compliance, and enforcement activities. It aims to ensure that the public has timely access to safe and effective pharmaceutical drugs and that those who need to know of safety concerns are informed.

We examined how Health Canada regulates clinical trials of new pharmaceutical drugs and reviews submissions seeking approval of new drugs for sale in Canada or of changes to drugs already on the market. We also examined how the Department monitors product safety and ensures that potential safety concerns are communicated to health care professionals and the public. In addition, we looked at how Health Canada enforces industry compliance with regulatory requirements governing the testing, production, and sale of drugs. We did not examine the soundness of the Department's regulatory decisions or the safety or efficacy of drugs.

The period under audit for this chapter was 1 January 2009 to 31 December 2010. Audit work for this chapter was substantially completed on 31 May 2011.

Why it's important

There are about 13,000 prescription and non-prescription drugs on the Canadian market. Pharmaceutical drugs play an important role in Canada's health care system and economy. In 2008, the Canadian retail market for prescription and over-the-counter drugs was valued at about $28 billion, with prescription drug purchases accounting for

almost 84 percent of total retail drug expenditures. According to IMS Brogan, a well-recognized provider of data to Health Canada and the pharmaceutical industry, about 505 million prescriptions were dispensed by Canadian retail pharmacies in 2010.

With an aging population, the role of pharmaceutical drugs is expected to grow as researchers come up with new drug therapies to replace earlier treatments or provide new options where no treatment existed before. Canadians who purchase and consume pharmaceuticals authorized for sale in Canada rely on the government and industry to monitor the safety of these products. Health Canada has a responsibility to help protect the public against undue health and safety risks from the use of pharmaceutical drugs.

What we found

- The Department does not take timely action in its regulatory activities, with the exception of its review of two types of drug submissions. In particular, the Department is slow to assess potential safety issues. It can take more than two years to complete an assessment of potential safety issues and to provide Canadians with new safety information.
- The Department received 4,400 drug submissions in 2009 and 2010. It has put in place processes and procedures to ensure that its drug reviews are consistent and high quality. However, it has not assessed whether these processes and procedures have been consistently interpreted and applied across its four review bureaus.
- Health Canada does not disclose information on drug submissions that it has rejected or information on the status of the drugs it has approved with conditions. In addition, the Department has not acted on its long-standing commitment to disclose more information about clinical trials it has authorized. This increases the risk that Canadians may be unaware of new treatment options or may unknowingly participate in an unauthorized trial.
- Health Canada's conflict-of-interest guidelines and Code of Conduct are consistent with government policy on conflict of interest. However, unlike another major regulator of pharmaceutical drugs and some federal departments that have developed conflict-of-interest requirements for specific work assignments, the Department has not determined what measures are necessary for its review activities.

The Department has responded. The Department agrees with all of our recommendations. Its detailed responses follow the recommendations throughout the chapter.

Introduction

Regulating pharmaceutical drugs in Canada

4.1 Each day, Canadians and their health care providers use pharmaceutical drugs (herein referred to as drugs) that have been approved by Health Canada to treat or prevent an array of diseases and disabling physical conditions. Enabling timely access to safe and effective drugs, and ensuring that these products remain safe and effective, is critical to improving and maintaining the health of Canadians.

4.2 Drugs are regulated under the *Food and Drugs Act*, which is administered by Health Canada. The Department defines pharmaceutical drugs as synthetic products made from chemicals, including

- prescription and non-prescription drugs;
- disinfectants; and
- products, such as sunscreens and antiperspirants, that are usually low risk.

4.3 There are about 13,000 drugs on the Canadian market, many of which are critical to high-quality health care. Canadians were expected to spend about $31 billion on these drugs in 2010. According to IMS Brogan, a well-recognized provider of data to Health Canada and the pharmaceutical industry, about 505 million prescriptions were dispensed by Canadian retail pharmacies in 2010.

4.4 Under the *Food and Drugs Act* and its accompanying regulations, Health Canada, as federal regulator, is responsible for assessing and monitoring the safety and efficacy of drugs marketed in Canada. The Department carries out these responsibilities through various regulatory activities that are designed to evaluate and monitor the safety, efficacy, and quality of drugs before and after they are marketed. Some of the costs of these activities are shared with industry, but others, such as reviewing clinical trial applications and compliance and enforcement activities for clinical trials, are funded solely by the Department. In the 2009–10 fiscal year, Health Canada spent about $80 million in direct program costs and employed approximately 700 full-time employees for drug regulation. The Department received about $33 million in fees from the pharmaceutical industry during the same period.

Stakeholders in pharmaceutical drug safety

4.5 There are several important stakeholders whose participation in the regulatory system is critical to supporting the safe and effective use of drugs.

4.6 **The Canadian public.** Canadians rely on Health Canada to approve drugs of demonstrated safety, quality, and efficacy and to work with the pharmaceutical industry to disseminate safety and usage information that is accurate and up to date. Canadian volunteers participating in clinical trials also rely on the Department to verify that authorized trials are designed appropriately, so they are not exposed to unnecessary risks.

4.7 **Health care professionals.** Health care professionals play an important role in promoting the appropriate use of drugs. To provide the public with information on the risks and benefits of specific drugs, health care professionals rely on Health Canada and drug manufacturers to disseminate safety and usage information that has been officially approved and that is accurate and up to date.

4.8 Health care professionals can also play a role in monitoring the continued safety of approved drugs. They are often the first to become aware of serious adverse drug reactions, and this makes them a critical source of safety information. Health Canada asks them to pass on this information when it comes to their attention, either to the manufacturer or directly to the Department. By doing so, they contribute to the evolving knowledge of a product's risks and benefits.

4.9 **Pharmaceutical industry.** The legal responsibilities of the pharmaceutical industry are outlined in the *Food and Drug Regulations*. The regulations place significant responsibility on the industry to protect the health and safety of the public. For example, the pharmaceutical industry is required to obtain authorization from Health Canada before conducting clinical trials of unapproved drugs. In its drug submissions to the Department, the industry is required to provide evidence that a drug meets safety, efficacy, and quality requirements. After the Department has approved a drug for sale, manufacturers are required to report all serious adverse drug reactions to Health Canada and to maintain the quality of their product. Manufacturers are also responsible for communicating new safety information about their products to health care professionals and consumers.

Health Canada's regulatory approach

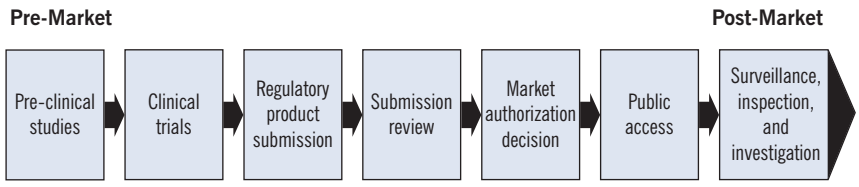
4.10 Health Canada's approach to the regulation of drugs focuses on well-defined points in the regulatory process that lead to a drug's marketing approval. However, after the Department has authorized a drug for sale, it has limited regulatory authority to require label changes that address new safety information or to require manufacturers to undertake additional post-market studies. Other regulators have greater post-market regulatory authorities. For example, the US Food and Drug Administration can legally require industry to propose labelling changes to reflect new safety information within 30 days of a request.

4.11 Health Canada's responsibilities include the following core activities:

- reviewing clinical trial applications, for clinical trials to be conducted in Canada;
- reviewing drug submissions from manufacturers for market authorization and for post-market changes;
- monitoring the safety of drugs in the Canadian market and communicating safety risks to health care professionals and the public, in collaboration with industry;
- enforcing the pharmaceutical industry's compliance with regulations, including those related to clinical trials, drug manufacturing, and the reporting of adverse drug reactions.

Exhibit 4.1 includes an overview of the regulatory process.

Exhibit 4.1 Regulatory process for drugs in Canada



Source: Health Canada

Focus of the audit

4.12 The focus of our audit was to determine whether Health Canada fulfilled its key responsibilities related to clinical trials, submission reviews, and post-market activities for the regulation of drugs.

4.13 We examined whether the reviews of clinical trial applications and pharmaceutical submissions were timely and whether the Department had established processes to support the timely, consistent, and high-quality review of drug submissions. We examined the steps the Department took to support the transparency of authorized clinical trials and its reviews, and the systems it implemented to manage potential conflicts of interest. We looked at how the Department monitored the safety of drugs in clinical trials and of drugs that had already been marketed, and whether it communicated safety concerns to health care professionals and Canadians in a timely manner. Finally, we examined the Department's methods for verifying the regulatory compliance of the pharmaceutical industry.

4.14 We did not examine authorized clinical trials to determine whether they were safe for the participants. We did not examine completed reviews of drug submissions to determine whether drugs approved by the Department were safe or effective or whether they were reviewed in a consistent manner. We did not examine the risks and benefits of marketed drugs.

4.15 More details about the audit objectives, scope, approach, and criteria are in **About the Audit** at the end of this chapter.

Observations and Recommendations

Regulating clinical trials

4.16 Clinical trials are experiments involving volunteer participants that are used to determine whether a drug is safe and effective and what side effects are associated with its use. Parties seeking to conduct clinical trials in Canada must submit a clinical trial application to Health Canada, except for clinical trials on drugs that are already on the market and are being tested to treat conditions for which they were authorized.

4.17 In 2001, the government revised the *Food and Drug Regulations* to strengthen protection for clinical trial participants. Health Canada also developed a national inspection program to verify that clinical trials conducted in Canada comply with these regulations, which were designed to protect the participant's safety and to generate high-quality

clinical data. The Department estimates that there are 4,000 active clinical trial sites (many sites are testing the same drug) in the country each year. If its inspectors identify significant non-compliance with the regulations, the Department can require immediate corrective action or, if necessary, revoke the trial's authorization.

Clinical trial applications and amendments were reviewed in a timely manner

4.18 In 2009 and 2010, Health Canada reviewed about 2,600 applications, and about 1,800 amendments to clinical trials, to assess whether the proposed trial or amendment posed undue risks to trial participants. Under the *Food and Drug Regulations*, if Health Canada does not review applications and amendments within 30 days, the trial can proceed or the amendment can be implemented by default. In addition, for selected clinical trial applications and amendments, the Department established a 7-day accelerated review target.

4.19 To determine the timeliness of its reviews of clinical trial applications and amendments in 2009 and 2010, we examined whether the Department was meeting the 30-day and 7-day timelines. We reviewed Health Canada's performance reports and assessed the completeness and accuracy of the data used to create these reports. We also examined management reports on program performance for the period under audit, analyzed data, and interviewed key officials. We found that the reviews of clinical trial applications and amendments were timely. The Department made all of its review decisions within the required 30-day period and met the 7-day target for selected clinical trial applications and amendments 90 percent of the time.

Additional steps are needed to strengthen a risk-based approach to oversee clinical trials

4.20 **Monitoring adverse drug reactions.** We examined whether Health Canada had established a risk-based approach to monitor **adverse drug reactions** in clinical trials. The *Food and Drug Regulations* require that clinical trial sponsors, such as drug companies and hospitals, inform the Department of all serious, unexpected adverse drug reactions for drugs being tested in Canadian clinical trials—regardless of whether the adverse drug reaction occurred at a trial site in Canada or in another country. The number of reported adverse drug reactions in clinical trials has increased dramatically over the past several years—43,000 in 2007, 88,000 in 2009, and 115,000 in 2010. According to the Department, about 95 percent of these reports are from foreign sources.

Adverse drug reaction—Any noxious and unintended response to a drug that is caused by the administration of any dose of the drug.

4.21 Monitoring and assessing adverse drug reactions is important for ensuring that Canadians participating in clinical trials are protected and fully informed of potential safety risks. Monitoring the safety of the 700 drugs that are tested in clinical trials in Canada each year also provides the Department with information that can be used by drug reviewers, clinical trial inspectors, and officials responsible for monitoring the safety of marketed drugs.

4.22 We reviewed the Department's procedures to determine whether it had established a risk-based approach for monitoring and assessing adverse drug reaction reports.

4.23 We found that Health Canada receives all adverse drug reaction reports by fax or courier and manually enters them into its adverse drug reaction database for clinical trials. The process is labour intensive, and it uses resources that could otherwise be used to assess potential safety issues raised in these reports. A description of how the Department expects to address this issue can be found in paragraph 4.75.

4.24 Due to the significant number of drugs in clinical trials each year, the volume of reports received, and the labour-intensive process in place, it is important that Health Canada have a risk-based approach to monitoring drugs in these trials. Officials told us that assessment officers were monitoring drug reaction reports from the trials that pose the highest risks, such as early-phase clinical trials of drugs not previously tested and trials that include vulnerable populations (for example, children). However, at the time of our audit, there were no standard operating procedures for its monitoring activities to ensure that the Department consistently focused on the trials that posed the greatest risk.

4.25 When the Department receives adverse drug reaction reports that indicate there may be a safety issue with a drug, officials may choose to fully assess the adverse reaction and its relationship to the drug. The assessment may result in recommendations being issued to ensure that risks are communicated to and, if possible, reduced for clinical trial participants. While officials told us that hundreds of potential safety issues are awaiting assessment, we found that, at the time of our audit, the Department had not documented its criteria for prioritizing its assessment of these potential safety issues based on the risks posed to clinical trial participants.

4.26 **Inspecting clinical trial sites.** We examined Health Canada's approach to clinical trial inspections to determine whether its compliance and enforcement activities focused on those trials that

posed the greatest risk. The Department inspects Canadian clinical trial sites to verify that authorized trials comply with the *Food and Drug Regulations*, so the rights and safety of trial subjects are respected. It also verifies that the data generated by the trial site is of high quality, which is important because this data can be used to support submissions for new drugs seeking market authorization. The June 2010 draft Compliance and Enforcement Risk Evaluation Guide: An Approach to Decision Making, by the Health Product and Food Branch Inspectorate, specifies that compliance and enforcement activities associated with a regulated product or activity need to be appropriate and proportional to the risk posed.

4.27 To determine whether compliance and enforcement activities for clinical trials were risk-based, we reviewed the Department's clinical trial inspection strategy, its performance reports, and its procedures for inspections. We also reviewed finalized inspection reports for the six non-compliant clinical trials identified in 2009 and 2010. We assessed whether the Department obtained assurance that instances of non-compliance were addressed.

4.28 We found that Health Canada had developed a risk-based inspection strategy that included criteria to help inspectors determine which clinical trial sites to inspect. The strategy required that inspectors consider a number of potential risk factors, including the following:

- number of clinical trials conducted at the site,
- number of subjects enrolled in the specified clinical trial,
- number of serious unexpected adverse drug reactions at the clinical trial site, and
- observations made during past inspections.

4.29 However, we also found that Health Canada does not regularly collect all of the information necessary to assess these factors and to make comparative risk-based decisions. Because clinical trial sponsors are not required to submit up-to-date information on clinical trial sites, inspectors must call each site directly to find out the current status of the clinical trial site and the number of participants enrolled.

4.30 Officials told us that acquiring this information through direct contact with each clinical trial site is inefficient and that a significant amount of time is devoted to identifying potential inspection sites. Thus, inspectors have up-to-date information only for sites that they call and are unable to compare the risks posed by all sites.

4.31 Health Canada's strategy is to inspect two percent (that is, about 80 out of 4,000) of Canadian clinical trial sites in any given year. The Department told us that this target is consistent with the approaches taken by other major regulators. We found that the Department completed 52 inspections in 2009 and 50 in 2010. Officials indicated that the target (of 80 per year) could not be met because of a lack of resources and the reallocation of existing resources to other programs.

4.32 Since 2006, Health Canada has issued nine inspection reports with non-compliance ratings—six of which were issued in 2009 and 2010. We reviewed these six reports to determine whether the Department verified that instances of non-compliance with the *Food and Drug Regulations* were addressed. Depending on the nature of identified deficiencies, corrective actions may be required to protect the safety of clinical trial participants and to ensure the quality of clinical trial data.

4.33 For these six reports, we found that Health Canada took between 56 and 142 days to officially notify regulated parties that they were not compliant with the *Food and Drug Regulations* and to officially request corrective actions to address all identified deficiencies. The Department has not established timelines for issuing these notifications, but regulated parties are required to propose corrective actions within four weeks of receiving an official notification of non-compliance.

4.34 Health Canada also reviews the adequacy of corrective actions proposed by regulated parties, but it has not set timelines for this review, either. During our audit, the Department reviewed proposed corrective measures for two non-compliant inspection reports and took about 110 days for each review. Officials told us that, during this time, the Department requested and reviewed additional information provided by regulated parties.

4.35 **Recommendation.** Health Canada should strengthen its risk-based approach for monitoring and assessing clinical trial adverse drug reaction reports and for inspecting clinical trial sites, so potential safety issues are mitigated.

The Department's response. Agreed. The Department is strengthening its risk-based approach to monitor and assess clinical trial adverse drug reaction reports and clinical trial inspections. A detailed standard operating procedure and strategy guide has been developed to prioritize the review of individual adverse drug reaction reports. This approach was implemented on 4 July 2011.

The Department expects to have completed a review of the existing risk-based process for selecting clinical trial inspection sites by fall 2011. This review will be used to assess the effectiveness of the existing process and to inform the development, documentation, and implementation of an enhanced process.

4.36 **Recommendation.** Health Canada should establish timelines for officially notifying clinical trial sites of non-compliant ratings and for reviewing proposed corrective measures to verify compliance with the *Food and Drug Regulations*.

The Department's response. Agreed. The Department is currently reviewing and revising its existing standard operating procedure for conducting clinical trial inspections. This revised standard operating procedure will emphasize establishing timelines for key steps in the inspection process, including notification of non-compliant ratings and the review of proposed corrective measures. This work will be completed by 31 March 2013.

Authorized clinical trials were not disclosed publicly

4.37 We examined steps taken by Health Canada to support the transparency of authorized clinical trials. In 2004, the House of Commons Standing Committee on Health recommended that the Department create a ". . . public database that provides information on trials in progress, trials abandoned and trials completed." In its 2007 Blueprint for Renewal II: Modernizing Canada's Regulatory System for Health Products and Food, the Department committed to enhancing public access to clinical trial information. Without this information, Canadians with life-threatening diseases may not become aware of trials that could offer new treatment options, and may not be able to verify whether the Department has authorized advertised trials.

4.38 We found that, despite commitments to increase the transparency of authorized clinical trials, the amount of information Health Canada made available to Canadians had not changed. There remains no definitive, publicly accessible source of information on clinical trials authorized by the Department.

4.39 For example, in 2008, Health Canada became aware of an unauthorized clinical trial when it was contacted by parents whose child was enrolled in the trial and who had concerns about the safety of the drug being tested. The physician running the trial was not based in Canada but was recruiting Canadian participants. According to files compiled by Health Canada during its review of the complaint,

advertisements for the trial claimed that the Department had authorized the trial. It was not until the parents contacted the Department with their concerns that they learned that it had not, in fact, authorized the trial. Electronic access to a listing of trials authorized by the Department would allow Canadians to consult official information, to verify claims made by other parties, and to make fully informed decisions.

4.40 In 1999 and 2004, parliamentary committees requested that Health Canada report annually on the findings of clinical trial inspections. Although openness and transparency are key aspects of its strategic and operational plans, the Department reported publicly only on its inspection activities in 2003 and 2004. For the past two years, it planned to publish a summary of its inspections on its website. At the time of our audit, a summary report on the clinical trial inspections conducted between 2002 and 2010 had been drafted but not published.

4.41 **Recommendation.** Health Canada should fulfill long-standing commitments to enhance public access to information on authorized clinical trials, including the results of its clinical trial inspections.

The Department's response. Agreed. The Department will develop policies on enhancing public access to information on authorized clinical trials that respect privacy rights and legislation. Work began in 2011 and will be completed by 31 March 2013.

The Department commits to publishing periodic reports regarding clinical trial inspections, to provide stakeholders and the public with a summary view of its inspection findings by 31 March 2012.

Reviewing drug submissions

4.42 Health Canada received about 4,400 drug submissions in 2009 and 2010. The Department reviewed pre-market submissions to determine whether claims made by industry regarding a drug's safety, efficacy, and quality were supported by sufficient evidence.

4.43 Submissions for new drugs that comprise chemicals that have not been available for a long period of time (typically, prescription drugs) must include a significant amount of data from clinical trials. Submissions for drugs that have been available for longer and have established safety records (typically, over-the-counter drugs) do not usually require as much data.

4.44 Because the safety of each drug is not absolute, Health Canada must weigh the potential benefits and risks of those seeking access to the Canadian market to determine whether the risks are acceptable.

Post-market submissions are submitted when manufacturers wish to make changes to a label or manufacturing method for a product that has already been marketed.

Health Canada does not meet its own service standards for reviewing drug submissions

4.45 Health Canada reviews a variety of pre-market submissions to determine whether they include sufficient evidence to support the pharmaceutical industry's claims about drug safety, efficacy, and quality. In consultation with the pharmaceutical industry, the Department developed service standards for these reviews in 1996 (Exhibit 4.2).

4.46 To determine the timeliness of its review decisions, we examined whether the Department was meeting its own service standards for reviewing pharmaceutical submissions. We also examined management reports related to program performance for the period under audit, analyzed data, and interviewed key officials.

4.47 We found that in 2009 and 2010, Health Canada consistently met its service standards for timely reviews of supplemental new drug submissions. However, it did not consistently meet its service standards for reviewing most of the other submission types. The Department's performance for reviewing generic drugs, over-the-counter drugs that required a clinical review, and post-market change submissions was particularly poor (Exhibit 4.2).

4.48 We found that reviews completed in 2010 that did not meet service standards took significantly longer than the standard to complete. The following are examples:

- Reviews of abbreviated new drug submissions (generic drugs) that did not meet service standards took, on average, 353 days (173 days longer than the 180-day standard).
- Reviews of DIN-A submissions (primarily over-the-counter drugs) that did not meet service standards took, on average, 539 days (329 days longer than the 210-day standard).
- Reviews of post-market manufacturing and safety-related labelling change submissions that did not meet service standards took, on average, 251 and 158 days, respectively (161 and 68 days, respectively, longer than the 90-day standard).

Exhibit 4.2 **Health Canada is not meeting its own service standards for reviewing most drug submissions**

Submission type	Description	Service standard for first review decision*	Percentage that meet service standards (target 90%)	
			2009	2010
New drugs				
New drug submission	Required for new drugs that have not been sold in Canada for a sufficient time and in sufficient quantity to establish their safety and effectiveness—includes clinical trial information and details on production, packaging, labelling, conditions for use, and side effects	300 calendar days	70%	70%
Supplemental new drug submission	Required if • substantial changes are made to a drug previously approved as a new drug submission, including dosage form, drug strength, method of manufacture, and labelling; or • the manufacturer wishes to expand the diseases or conditions the product is approved to treat	300 calendar days	92%	91%
Generic drugs				
Abbreviated new drug submission	Required for new generic drugs; submissions must include evidence that the generic is equivalent to the existing patented drug (delivers the same amount of medicinal ingredient and at the same rate)	180 calendar days	36%	12%
Supplemental abbreviated new drug submission	Required if changes are made to a new generic product that was previously approved as an abbreviated new drug submission, including method of manufacture, labelling, recommended route of administration, or a new indication	180 calendar days	71%	5%
Over-the-counter drugs				
Drug identification number (DIN) applications	A DIN-A application is used most commonly for over-the-counter drugs that have established safety records but that require additional supporting data and a clinical review.	210 calendar days	19%	36%
	A DIN-F application is used most commonly for over-the-counter drugs that comply with existing drug labelling and that do not require additional supporting scientific data.	45 calendar days	93%	83%
Post-market (notifiable) changes				
Chemistry or manufacturing changes	Manufacturers must inform Health Canada of changes to a drug that could adversely affect its safety, purity, potency, or effectiveness.	90 calendar days	9%	14%
Labelling and product monograph changes	Manufacturers must inform Health Canada of changes to a drug that could adversely affect its safety, purity, potency, or effectiveness.	90 calendar days	57%	70%

Note: These service standards exclude the screening times to assess the completeness of a submission.
* A first decision can result in a request for additional information from the manufacturer, a rejection of the submission, or an approval.

4.49 According to Health Canada, a number of factors can contribute to poor review performance. For example, drug reviewers are often required to perform duties other than reviewing submissions, such as

- assessing the potential health risks posed by defective or illegal products; or
- contributing to related **risk communications**, so the public is informed of potential safety risks.

Risk communication—The development and dissemination of information about potential or existing health risks, to enable patients and their health care professionals to make better informed decisions about their health.

4.50 We found that Health Canada has taken a number of steps to improve its review performance. Foremost among these was a new cost recovery framework, implemented in April 2011. The Department expects that the additional revenue, obtained by charging the pharmaceutical industry increased fees, will improve review times. The new user fees will be governed by the *User Fees Act*, which includes penalties (of up to 50 percent of the fees) for the Department if it does not meet its service standards. This means that the Department would receive less revenue from user fees, which could in turn reduce its resources for reviewing submissions.

4.51 We also found that the Department launched an initiative in June 2010 to develop a consistent approach to the use of foreign regulatory information in order to improve review efficiency. **Health Canada's four review bureaus** have each explored different approaches to reduce existing backlogs and to improve review performance, such as assessing workloads to determine the actual number of hours required to review drug submissions and the time spent on non-review activities. They expect this work will help streamline review processes and improve planning.

Health Canada's four review bureaus—Drug review responsibilities are divided among four review bureaus based on the type of review required, the drug's therapeutic class, and whether the drug will be available by prescription or over the counter.

Three clinical review bureaus are responsible for assessing drugs that treat specific diseases, such as cancer or HIV. The fourth bureau reviews submissions for generic drugs and reviews the manufacturing and chemistry component of all drug submissions. The four review bureaus comprise eleven more specialized review units.

4.52 Canadians and health care professionals benefit from timely access to safe and effective drugs. It is important that Health Canada take the necessary time to properly evaluate a drug for safety and efficacy, but delays in approving new drug submissions mean that access to the potential benefits of these drugs is delayed. The untimely review of abbreviated (generic) new drug submissions may limit access to more affordable treatments. The delayed review of post-market change submissions, particularly those for labelling changes to address potential safety issues identified by the pharmaceutical industry or by the Department, means that new safety information may not be provided to Canadians as quickly as possible.

4.53 **Recommendation.** Health Canada should ensure that it meets service standards for the review of all drug submission types—by giving due consideration to the appropriate allocation of additional resources

from increased fees charged to industry, to the use of foreign regulatory information, and to streamlining its review processes.

The Department's response. Agreed. Revenues from recently updated user fees will allow the Department to meet its well-established and internationally recognized performance standards. The Department will closely monitor its performance. It will continue to seek process efficiencies, such as increasing the leverage of external scientific expertise and the use of foreign regulatory information. The Department will begin piloting an approach to enhance and formalize the use of foreign reviews through standard operating procedures and guidance for industry in the fall of 2011 and will complete an evaluation of the pilot by 31 March 2014.

Health Canada has not assessed whether its review bureaus interpret and apply review procedures and guidelines consistently

4.54 We examined whether Health Canada had established a quality assurance system for its review of drug submissions. In a strategic plan for these reviews—Therapeutic Products Directorate Strategic Plan, 2006–2009, The Way Forward—the Department acknowledged the importance of consistent, timely, and high-quality review decisions.

4.55 We found that the Department has the following key components of a quality assurance system:

- standard operating procedures,
- guidelines for drug reviewers,
- review templates,
- training programs, and
- management review of individual files.

4.56 However, we also found that Health Canada has not assessed whether review procedures, guidelines, and templates were consistently interpreted and applied across the four different review bureaus responsible for conducting reviews of drug submissions. Such an assessment would allow the Department to identify inconsistencies between the different review bureaus that may affect the timeliness and quality of review decisions.

4.57 **Recommendation.** Health Canada should regularly assess whether the procedures and guidelines, which were established to ensure timely, consistent, and high-quality review decisions, are interpreted and applied consistently by all four review bureaus.

The Department's response. Agreed. The Department will develop a system to regularly assess and ensure the use of procedures established to ensure timely, consistent, and high-quality review decisions by 31 December 2012. Implementation of the system, which will include assessment of compliance with procedures and consistency of interpretation across organization review units, and necessary corrective mechanisms to ensure consistent use, will be completed by 31 December 2013.

More information on Health Canada's reviews of drug submissions needs to be made available to Canadians

4.58 We examined several of Health Canada's commitments to increase the transparency of review decisions and the amount of information it makes available to Canadians about approved drugs. These commitments are consistent with government-wide directives to foster understandable and responsive regulation through inclusiveness, transparency, accountability, and public scrutiny. It is important that Canadians have access to information so they are able to make informed decisions about the drugs they use.

4.59 To determine whether Health Canada had fulfilled its commitments for increasing the transparency of review decisions, we examined the availability and the timeliness of the public disclosure of key documents to its website (product monograph, notice of decision, summary basis of decision) for all 34 **new active substances** approved in 2009 and 2010. We found that, while it had met its timelines for posting product monographs, the Department had not consistently met its timelines for posting notice of decision or summary basis of decision documents (Exhibit 4.3).

New active substance—A chemical not previously authorized for sale in Canada as a drug.

4.60 Health Canada occasionally attaches conditions to a drug's approval, asking the manufacturer to carry out additional post-market studies. We found that the Department does not disclose the timelines established for fulfilling these conditions, nor does it report on the progress made by manufacturers in fulfilling these conditions. We noted that the US Food and Drug Administration does provide updates on the status of post-market conditions.

4.61 Health Canada told us that, until recently, manufacturers were not asked to report regularly on their progress in fulfilling post-market conditions. Since June 2011, manufacturers have been asked to provide annual updates, but they are under no regulatory obligation to do so.

4.62 Health Canada is also not disclosing information on drugs that it rejects or on drugs that the manufacturer withdraws from the review

process. Health care providers have the discretion to prescribe a drug for conditions that the drug has not been authorized to treat. Therefore, it is important that they be informed when the Department rejects a marketed drug for a new use, so they understand the Department's concerns. We also noted that the European Medicines Agency, which is responsible for the scientific evaluation of medicines for use in the European Union, discloses information related to rejections and withdrawals of drug submissions.

Exhibit 4.3 The Department did not consistently meet its own timelines for posting review documents for drugs with new active substances

Document	Description	Posting timeline	Number reviewed	Number posted within the timeline
Product monograph	Describes the health claims, indications, and conditions for the safe and effective use of a drug. It also includes other important information, such as safety warnings, precautions, adverse reactions, and interactions with other drugs.	At the time of market notification	28*	• 28 met the timeline
Notice of decision	Outlines in a one-page summary the authorization received and general information related to the approved drug.	Within 6 weeks of drug approval	31**	• 20 met the timeline • 11 took an average of 3 weeks longer
Summary basis of decision	Outlines the scientific and benefit or risk considerations that factor into Health Canada's decision to approve a drug.	Within 20 weeks of drug approval	31**	• 15 met the timeline • 15 took an average of 12 weeks longer • 1 was not yet posted

* Five of the new drugs approved during the period subject to audit have not been marketed in Canada, and one of the new drugs was discontinued. Therefore, a product monograph was not required for these six drugs.

** Three new drugs approved in the period subject to audit were not considered to be new active substances. Therefore, they were not eligible for a Notice of Decision or a Summary Basis of Decision document.

4.63 Recommendation. Health Canada should disclose information related to new drug approvals in a timely manner and improve the transparency of "approvals with conditions," rejections, and withdrawals of new drugs so that Canadians and health care professionals can access information about these drugs.

The Department's response. Agreed. The Department will improve the transparency of approvals with conditions, rejections, and withdrawals to the Canadian public. The Department will consult with stakeholders in fall 2011 about expanding its public communications on post-approval decisions for marketed health products to include information on approvals with conditions, rejections, and withdrawals, with a view to disclosing additional information by June 2012.

Health Canada has not determined what measures are necessary to manage conflict-of-interest risks for drug reviewers

4.64 In the federal government, "conflict of interest" refers to a conflict between the public service duties and private interests of public servants. In the 2010 Fall Report of the Auditor General, Chapter 4, Managing Conflict of Interest, we noted that

> . . . conflicts of interest bring into question the integrity and fairness of decisions made by public servants. If not properly addressed, conflicts of interest can increase the level of distrust and cynicism toward government and, over time, impact the legitimacy and effectiveness of government actions.

4.65 The government's Values and Ethics Code for the Public Service requires that departments establish measures to manage conflicts of interest. To determine whether Health Canada had systems to manage conflict-of-interest risks to the drug submission review process, we examined its Code of Conduct and its conflict-of-interest guidelines, and interviewed key entity officials. The audit was not designed to find cases of officials being in a conflict of interest, and we did not find any such cases.

4.66 We found that Health Canada's code of conduct and conflict-of-interest guidelines are consistent with the government's Values and Ethics Code for the Public Service. However, in 2010, the Department had not complied with the code's requirement to issue an annual reminder to employees of their conflict-of-interest obligations and, at the time of our audit, the Department had not issued this reminder for 2011.

4.67 Compliance measures beyond those specified in the Values and Ethics Code for the Public Service are permitted if a department believes they are necessary to address its specific responsibilities. Officials responsible for reviewing drug submissions routinely handle commercially sensitive information that could be used for personal gain, and they are directly involved in making decisions that could have significant commercial benefits. However, we found that the Department has not determined what measures are necessary to address these risks.

4.68 In our 2010 Fall Report, Chapter 4, Managing Conflict of Interest, we noted that some government departments had developed conflict-of-interest requirements for specific work assignments. For example, Natural Resources Canada requires staff assigned to the management of contribution agreements to acknowledge in writing

that they understand what to do to avoid and disclose conflicts of interest for each agreement in which they are involved.

4.69 We also noted that the European Medicines Agency requires that its employees' declarations of interests be updated annually and that its drug reviewers' declarations be checked each time they are assigned to review a new drug submission.

4.70 **Recommendation.** Health Canada should assess the risks posed by conflicts of interest to the drug review process, determine what measures are necessary to manage these risks, and implement those measures.

The Department's response. Agreed. The Department requires disclosure of potential conflicts of interest at the initiation of employment, and employees are subject to the Values and Ethics Code for the Public Service. The Department will determine if there are any particular risks posed by potential conflicts of interest in the drug review process by 31 March 2012 and, if necessary, develop and implement additional measures by 30 September 2012.

Monitoring post-market safety

4.71 Health Canada monitors the safety of marketed drugs by collecting, analyzing, and assessing domestic adverse drug reaction reports that are submitted by the pharmaceutical industry, health professionals, and consumers. The Department also collects foreign adverse drug reaction reports that are submitted by the pharmaceutical industry. In addition, it reviews scientific literature, as well as actions taken by other regulators, to address safety concerns identified from these sources. The Department uses this information to determine whether further action is needed to protect the public, including

- conducting full assessments of potential safety issues,
- recommending that manufacturers revise product labels and working with manufacturers to implement these revisions, and
- communicating new safety information to health care providers and the public.

4.72 We examined Health Canada's approach to monitoring the safety of drugs marketed in Canada. According to its post-market surveillance strategy, the Department is responsible for ensuring that the benefits of using a drug outweigh the risks. It fulfills this responsibility by gathering and assessing safety information, from a

variety of sources, and by implementing measures necessary to reduce the safety risks associated with marketed drugs. To determine whether the Department uses a risk-based approach for monitoring marketed drugs, we examined its processes for obtaining, assessing, and acting on drug safety information.

Health Canada has recently taken additional steps to actively monitor drug safety

4.73 In 2010, Health Canada received about 30,000 domestic adverse drug reaction reports and about 330,000 foreign reports. The vast majority of these reports were submitted by the pharmaceutical industry, which is required to report adverse reactions to the Department. Adverse drug reaction reports are an important component of monitoring drug safety.

4.74 We found that Health Canada does not have mechanisms to receive these adverse reaction reports electronically, and it has not entered the foreign reports it receives each year in its post-market adverse drug reaction database. Adverse drug reactions captured in this database may help identify potential safety issues. Although the Department can consult foreign adverse drug reaction reports when necessary, it does not regularly analyze these reports or search them electronically to detect emerging safety issues. Canada's small population reduces the likelihood of serious, rare adverse drug reactions being identified in this country; therefore, the capacity to search and analyze foreign reports electronically would contribute to more comprehensive safety monitoring.

4.75 The Department expects to begin electronic reporting pilots in the 2011–12 fiscal year. When electronic reporting is fully implemented, the Department believes it will have the capacity to electronically capture and analyze the foreign reports it receives each year.

4.76 We found that Health Canada had recently implemented strategies to electronically search its domestic adverse drug reaction reports, to better detect adverse reactions for specific drugs, and to systematically monitor those adverse reactions that are rare, serious, and often linked to marketed drugs. A similar approach to monitoring adverse drug reaction data for vulnerable populations (for example, children) has yet to be implemented.

4.77 Due to the limitations of adverse drug reaction reports, the World Health Organization has encouraged regulators to incorporate active surveillance into their monitoring activities. We found that,

since 2009, Health Canada has taken several steps to increase active monitoring, including the following:

- establishing formal working groups to systematically consider potential safety issues that were identified by other regulators, reported in scientific journals, or identified by industry;
- implementing an inspection program to ensure that companies comply with regulatory requirements to report adverse drug reactions; and
- reviewing **risk management plans** voluntarily submitted by the pharmaceutical industry, as part of some drug submissions, which may identify potential safety issues and include manufacturers' commitments to actively monitor the drug.

Risk management plan—A set of monitoring activities and interventions by the manufacturer designed to identify, characterize, prevent, or minimize risks relating to drugs and designed to assess the effectiveness of those interventions.

4.78 The Department has acknowledged that it had not yet set up monitoring systems to identify adverse drug reactions in patients who are taking certain drugs or to detect adverse reactions in health care settings, such as emergency departments, where those suffering an adverse reaction may seek treatment. However, the Department has recently launched an initiative to identify more active surveillance activities and to determine their potential value.

Health Canada's assessment of, and response to, potential safety issues is not timely

4.79 **Assessing safety issues.** Health Canada uses information obtained through its monitoring activities to assess whether there may be a safety issue with a specific drug. Depending on the results of its assessment, it may recommend changes to the drug's label, issue a risk communication to the public or health care professionals about the risks of using the drug, or do both.

4.80 In certain instances, Health Canada may also withdraw a drug's market approval. It is important to note that the Department has indicated that after it has approved a drug for sale, it has limited authority to require that manufacturers update drug labels or issue risk communications about new safety concerns. Overall, we found that the Department did not assess potential safety issues, detected through its monitoring activities, in a timely manner. Therefore, changes to drug labels and risk communications were also not timely.

4.81 In 2009 and 2010, Health Canada completed 99 assessments of potential safety issues, which were identified through its post-market monitoring activities. The Department had established draft risk-based timelines for these assessments. Of the 99 assessments, 54 resulted in recommendations about updating the labelling for specific drugs or

classes of drugs and issuing risk communications. Almost half of the assessments that resulted in recommendations were triggered by actions taken by other regulators (Exhibit 4.4).

Exhibit 4.4 The greatest number of Health Canada safety recommendations resulted from actions by foreign regulators

Source of safety assessment that resulted in recommendation	Number of recommendations
Actions of foreign regulators	25
Safety information from scientific literature	15
Adverse drug reaction reports, and previous Health Canada assessments of potential safety issues	9
Safety information provided by manufacturers	5
Total	**54**

4.82 We reviewed all 54 of these assessments (Exhibit 4.5). It is important that these assessments be completed in a timely manner, so if there are safety risks they can be confirmed and communicated to Canadians.

Exhibit 4.5 Health Canada does not consistently meet its targets for completing safety assessments

Priority rating	Performance target	Assessments reviewed	Actual performance	
			Met	Not met
High—Potential safety issues that, if confirmed, will likely require an intervention. These include adverse drug reactions that were unknown, unlabelled, or insufficiently labelled.	80 working days	0	0	0
Medium—Potential safety issues that are not as serious or not as unexpected, but still require a comprehensive assessment. If confirmed, these safety issues are likely to require labelling changes.	130 working days	29	16	13
Low—Potential safety issues that are well known or labelled. These issues are not likely to affect the way a drug is used.	200 working days	25	18	7
Total		**54**	**34**	**20**

4.83 Of the 54 assessments we examined, 34 were completed within the established timelines. However, the Department's approach to measuring its performance does not consider the following:

- amount of time a potential safety issue may wait before an assessment begins;
- amount of time an assessment may be placed on hold;
- amount of time needed to obtain additional information from external parties (for example, manufacturers or other regulators); and
- total number of calendar days, instead of working days, taken to complete the assessment.

4.84 When these factors are considered, Health Canada took at least one year to complete 34 of its 54 assessments. In some cases, it took significantly longer. For example, 5 medium-priority assessments required more than two years to complete, and 1 of the 5 required more than three years to complete.

4.85 Although Health Canada did not conduct any high-priority safety assessments in 2009 and 2010, we noted that two drugs were voluntarily withdrawn by manufacturers from the Canadian market for safety reasons during that period. Both withdrawals occurred after new studies confirmed that the risks of using the drugs outweighed any benefits. One of these drugs was withdrawn by the manufacturer before the Department had completed an ongoing safety assessment, and the other was withdrawn without an assessment being conducted. In both cases, the Department publicly announced the withdrawals at approximately the same time as the US Food and Drug Administration.

4.86 Updating drug labels and communicating health risks. According to its post-market surveillance strategy, Health Canada is responsible for managing identified safety risks, which includes communicating health risks to health care professionals and the public, and working with manufacturers to update drug labels with the most recent safety information. Of the 54 safety assessments we examined, Health Canada had recommended 51 labelling updates and 24 risk communications. It is important that these recommendations are implemented so that health care providers and consumers have access to the most up-to-date safety information available.

4.87 We found that there is no systematic process to implement recommendations for labelling updates. This is important because officials responsible for making safety-related recommendations are not

the same officials responsible for working with the drug manufacturers to implement these recommendations. We found that the officials responsible for implementing recommendations often do not document whether they agree or disagree with recommended labelling updates or how they intend to implement the recommendations, including what the proposed timelines are for implementation.

4.88 Once the Department has decided to implement a recommendation to update a drug's label to include new safety information, its officials are responsible for starting the process, by notifying the manufacturer of the requested update. We found that the Department has not established timelines for issuing these notifications.

4.89 Health Canada needed to notify manufacturers about 38 of the 51 recommended label updates. It did not need to notify manufacturers about the other 13 because in some of those cases, the manufacturer had already updated the labelling, and, in others, the Department was already reviewing a manufacturer's submission to address the recommendation.

4.90 We found that for 12 of these 38 recommended updates, it took Health Canada between 3 and almost 20 months to issue notifications to manufacturers. We also found that the Department had not yet notified the manufacturer of another 6 recommended label updates, even though between 6 and 28 months had passed since the recommendations were first made. Officials told us that the Department may delay notifying manufacturers of requested label updates if it does not have the resources available to review all the submissions that will result from the request. For example, according to the Department, one label update that affects a class of drugs could generate well over 100 notifiable change submissions.

4.91 We also found that labelling recommendations are not directly communicated to the departmental officials who are responsible for working with the pharmaceutical industry to update labels for generic drugs. As a result, these officials may not be informed of key safety issues, and labels on generic drugs may not be updated in a timely manner. According to IMS Brogan, 57 percent of prescriptions dispensed by Canadian retail pharmacies in 2010 were for generic drugs. The case study on a label change for a drug to treat epilepsy shows the impact of not formally tracking safety recommendations—that is, how undefined processes and poor communications can result in inconsistent labelling between brand name and generic drugs.

Case study—Label change for a drug to treat epilepsy

In August 2009, Health Canada completed a safety assessment on a drug approved to treat epilepsy and migraine headaches, which was also used off-label to treat several psychiatric conditions and to promote weight loss. The completed assessment recommended that the drug's label be updated to reflect newly identified risks related to increased incidence of birth defects.

In September 2009, the Department sent a letter to the brand-name manufacturer of the drug requesting that the drug's label be updated to reflect this new safety information. In April 2010, the label for the brand name drug was revised.

According to Health Canada, generic drug manufacturers should update safety information so generic drug labels are consistent with those for brand-name drugs. The Department has a practice of alerting generic manufacturers when a brand-name drug revises its labelling to address new safety issues.

Health Canada officials responsible for working with the generic drug industry were not notified of the required labelling changes until February 2011—almost one year after the brand name drug changed its product monograph. Hence, the Department did not inform the 12 generic manufacturers with outdated product monographs of the need to update these documents until March 2011. The Department did not need to inform two other manufacturers of the drug, because they had already updated their product monographs. As of 31 May 2011, they remain the only generic drug manufacturers marketing this drug in Canada with updated product monographs.

4.92 Safety assessments may also recommend that risk communications be issued to inform the public of new drug safety information. We found that of the 24 recommended risk communications that we examined, 11 were not issued by Health Canada until six months after the assessment had been completed. In three cases, we found that the Department took more than a year to issue a recommended risk communication.

4.93 According to Health Canada, in less urgent cases, the Department does not issue a risk communication until a drug's label has been updated to reflect the most recent safety information.

4.94 As noted earlier, the Department does not complete its safety assessments, or notify manufacturers of requested label updates, in a timely manner, and it does not consistently meet its service standards for the review of notifiable change submissions (Exhibit 4.2). As a result, a significant amount of time can pass before recommended risk communications are issued to Canadians.

4.95 Overall, we found that for 11 of the 24 recommended risk communications that we examined, it took the Department more than two years to assess the potential safety issue, update the drug's label (where necessary), and issue the risk communication.

Case study—Delayed risk communication for two commonly used drugs

In 2006, the US Food and Drug Administration released a public risk communication stating that the therapeutic effectiveness of daily low-dose acetylsalicylic acid (ASA) therapy was potentially reduced when ibuprofen was taken at the same time. Health Canada started to assess this potential safety issue in January 2006 and finished in September 2009. It recommended that labels for products containing acetylsalicylic acid and ibuprofen be updated and that a risk communication be issued to inform Canadians of this new safety information. As of May 2011, not all labels for the several hundred affected products had been updated, and Health Canada had not issued the recommended risk communication.

4.96 **Recommendation.** Health Canada should improve the timeliness of safety assessments and the implementation of related recommendations to update labels and to issue risk communications, so Canadians and health care professionals can be informed of new drug safety information in a timely manner.

The Department's response. Agreed. The Department will improve the timeliness of safety assessments by fully implementing and respecting related performance standards by December 2013. This involves reviewing baselines for completing safety reviews.

4.97 **Recommendation.** Health Canada should establish a systematic process to manage safety assessment recommendations for marketed drugs, to ensure that recommendations are dealt with appropriately and in a timely manner.

The Department's response. Agreed. The Department will establish a systematic process to implement safety assessment recommendations for marketed drugs. The Department has already begun developing a standard operating procedure in this regard. The standard operating procedure will include new formalized tracking systems (currently under development) and necessary implementation procedures following a safety assessment recommendation. This will be in place by 31 March 2013.

4.98 **Assessing the effectiveness of risk communications.** In addition to communicating safety risks to Canadians in a timely manner, it is important for Health Canada to know whether its risk communications are effective and have an impact on targeted audiences. In Planning for Our Future: Federal Regulatory Post-Market Surveillance Strategy 2007–2012, the Department includes a commitment to evaluate the effectiveness of its risk management actions.

4.99 We found that Health Canada has not assessed the effectiveness of risk communications but has begun to examine this issue. For example, the Department commissioned a study of how health care professionals use its risk communications: specifically, the impact of these communications on prescribing patterns in Canada. Officials told us that assessing the impact of risk communications on behaviour is also challenging for foreign regulators, because there is no widely accepted approach to measuring the effectiveness of risk communications.

Enforcing compliance with the regulations

4.100 Health Canada's compliance and enforcement activities are conducted by inspectors in its regional offices. The Department maintains a national inspection program that examines the operations of various drug establishments, such as manufacturers, wholesalers, and distributors—to verify that the pharmaceutical industry is complying with the internationally accepted Good Manufacturing Practices, which are set out in the *Food and Drug Regulations*.

4.101 Serious deficiencies identified during an inspection can result in a request for a product recall or the suspension of an establishment licence. Health Canada also follows up on reported complaints or concerns, such as those related to the illegal sale of pharmaceutical drugs or the quality or safety of those available for sale. The Department also monitors the industry's implementation of product recalls.

Actions have been taken to make inspections of drug establishments more risk-based

4.102 Health Canada inspects Canadian drug establishments to verify that they comply with the good manufacturing practices required by the *Food and Drug Regulations*, which reduces the likelihood that Canadians will be exposed to substandard drugs. The Department's draft Compliance and Enforcement Risk Evaluation Guide: An Approach to Decision Making specifies that compliance and enforcement activities associated with regulated products or activities need to be appropriate and proportional to the risks.

4.103 We found that the Department has established risk-based inspection cycles for drug establishments based on the nature of their activities. For example, drug manufacturers were inspected every two years, whereas lower-risk establishments, such as distributors, were inspected every three years.

4.104 In June 2010, Health Canada completed a review of its drug establishment inspection program and recommended that the program

be more risk-based. As a first step, in April 2011, the Department eliminated renewal inspections that are normally conducted when annual establishment licences expire. It expected that this change would enable inspectors to focus on high-risk establishments, as opposed to those requiring an inspection as part of the licence renewal process. Other recommendations arising from this review were also being implemented.

4.105 **Foreign manufacturers.** According to Health Canada, approximately 80 percent of health products used by Canadians are manufactured in other countries. The Department established mutual recognition agreements with 26 international partners to ensure that drugs manufactured in these jurisdictions and imported into Canada comply with the Good Manufacturing Practices required by the *Food and Drug Regulations*.

Complaints about marketed drugs are not prioritized consistently

4.106 We examined whether Health Canada used a risk-based approach to follow up on complaints about drugs, and whether it verified compliance with the *Food and Drug Regulations*. The Department's draft Compliance and Enforcement Risk Evaluation Guide: An Approach to Decision Making specifies that compliance and enforcement activities associated with a regulated product or activity be appropriate and proportional to the risk. Verifying the regulatory compliance of marketed drugs is critical to ensuring that Canadians are not exposed to unsafe drugs.

4.107 To determine whether Health Canada used a risk-based approach, we

- reviewed its performance reports and standard operating procedures, for its compliance verification activities;
- interviewed its key officials in Ottawa and in its three largest regional operational centres; and
- reviewed a representative sample of 50 files related to drug-specific complaints that were also closed in 2009 or 2010.

4.108 In 2009 and 2010, the Department received almost 800 complaints concerning specific drugs from consumers, health care professionals, the pharmaceutical industry, and other stakeholders. Health Canada had established risk-based standard operating procedures for prioritizing reported cases of non-compliance to ensure that compliance and enforcement actions are initiated within specified timelines. However, we found that these procedures were not

implemented consistently. In 27 of the 50 complaint files we reviewed, we found that the Department had not prioritized these complaints using its standard operating procedures. Therefore, the Department could not demonstrate that compliance and enforcement actions were initiated in a timely manner. For 12 of the 23 complaints that were prioritized in accordance with procedures, we found that the Department had initiated compliance and enforcement actions within the established timelines.

4.109 **Recommendation.** Health Canada should consistently apply its risk-based standard operating procedures, so the priority of the drug complaints it receives is properly documented and addressed in a timely manner.

The Department's response. Agreed. The Department strives to ensure that complaints received are addressed in a timely manner and are properly documented. The Department will review its processes to ensure better documentation, conduct training sessions, and implement more robust performance monitoring by 31 March 2013.

Conclusion

4.110 We conclude that Health Canada has fulfilled its responsibilities for the timely review of clinical trial applications and amendments. However, it has not adequately fulfilled its key responsibilities for verifying the regulatory compliance of authorized trials. Although Health Canada has a risk-based clinical trial inspection strategy, it does not have all the information it needs to make comparative risk-based decisions about which sites to inspect, and it does not regularly report on its clinical trial inspection activities. The Department had also not met its clinical trial inspection target in 2009 or 2010. Furthermore, the Department does not document its approach to monitoring adverse drug reactions in clinical trials to ensure that it focuses on the trials that posed the greatest risk. It did not fulfill long-standing commitments to increase the transparency of authorized clinical trials.

4.111 Health Canada did not review most drug submissions within its established service standards and did not assess whether its four review bureaus consistently interpret and apply procedures designed to support timely, consistent, and high-quality reviews of drug submissions. The Department increased the amount of information publicly available on approved drugs and on its rationale for approving these drugs. However, this information could be timelier. The Department does not disclose information on drug submissions that were rejected or withdrawn.

4.112 Health Canada's conflict-of-interest guidelines are consistent with the government's Values and Ethics Code for the Public Service. However, in 2010, the Department had not complied with the code's requirement to issue an annual reminder to employees of their conflict-of-interest obligations. At the time of our audit, the Department had not yet issued this reminder for 2011, nor had it determined the necessary measures to address the conflict-of-interest risks specific to its review activities. Some federal government departments and a major regulator of pharmaceuticals have developed additional measures to manage conflicts of interest for specific activities.

4.113 Health Canada has not adequately fulfilled its key responsibilities for monitoring the safety of marketed drugs. It recently took steps to actively monitor drug safety, and it is developing the capacity to process and analyze foreign adverse drug reaction reports that it receives from the pharmaceutical industry. The Department developed a risk-based approach to assessing the safety issues it identified through its monitoring activities, and it has established timelines for this work. However, it does not complete these assessments or communicate safety concerns in a timely manner, and it has not established systematic processes for implementing the recommendations that result from these assessments.

4.114 Health Canada has fulfilled its key responsibilities for verifying the regulatory compliance of industry. It takes a risk-based approach to inspecting drug establishments and is working to strengthen this approach. However, although the Department developed a risk-based approach for following up on complaints about specific drugs, it does not apply it consistently.

4.115 In summary, we examined key Health Canada responsibilities involving timeliness, consistency, transparency, conflict of interest, and risk-based post-market activities. We found that the Department has not adequately fulfilled most of these key responsibilities related to clinical trials, submission reviews, and post-market activities for pharmaceutical drugs.

About the Audit

All of the audit work in this chapter was conducted in accordance with the standards for assurance engagements set by The Canadian Institute of Chartered Accountants. While the Office adopts these standards as the minimum requirement for our audits, we also draw upon the standards and practices of other disciplines.

Objectives

The overall audit objective was to determine whether Health Canada fulfilled its key responsibilities related to clinical trials, submission reviews, and post-market activities for pharmaceutical drugs.

The audit sub-objectives were to determine whether the Department fulfilled its key responsibilities for

- conducting timely clinical trial application reviews;
- supporting the transparency of authorized clinical trials, and verifying their regulatory compliance;
- conducting timely and consistent submission reviews;
- supporting the transparency of review outcomes;
- implementing systems to manage conflicts of interest;
- monitoring the safety of marketed pharmaceuticals;
- communicating safety concerns in a timely manner; and
- verifying the regulatory compliance of industry.

Scope and approach

Our audit focused on the three Health Canada directorates that are involved in the regulation of pharmaceuticals. We examined the timeliness of reviews for clinical trial applications and for drug submissions, received from the pharmaceutical industry, for market authorization and post-market changes. Where necessary, we conducted gap analyses to assess the completeness of the data used by the Department to measure its review performance. We also verified the accuracy of the Department's data by conducting a file review of a representative sample of clinical trial applications and drug submissions.

We also examined whether the Department had established the necessary quality assurance systems to support consistency among its review activities and what efforts it had made to ensure the transparency of clinical trials by disclosing information about those that were in progress, abandoned, or completed. We also reviewed various departmental initiatives to increase the transparency of its drug submission reviews.

We examined the Department's safety monitoring activities for drugs being tested in clinical trials and for those already marketed, to determine whether the Department completed its assessments and ensured that safety-related recommendations, such as labelling updates and risk communications, were implemented in a timely manner.

We also examined compliance and enforcement activities to determine whether the Department had employed a risk-based approach to its inspection of clinical trial sites and pharmaceutical establishments and to its follow-up of product-specific complaints or concerns it had received from various stakeholders. As part of this work, we examined a representative sample of complaints. The sample size was sufficient to conclude on the sampled population with a margin of error of +10 percent 18 times out of 20.

We interviewed key Health Canada officials involved with regulation of pharmaceuticals at headquarters and in the larger regional offices and met with representatives from the pharmaceutical industry and the health care field. We reviewed documentation, including regulations, strategic and operational plans, program reviews, and reports filed by the Department's inspectors in the field.

We did not examine the following:

- regulation of biologics (products derived from living sources, such as blood and vaccines), radiopharmaceuticals (radioactive products used to diagnose illness), or disinfectants;
- completed reviews of drug submissions to determine whether drugs approved by the Department were safe or reviewed in a consistent manner;
- regulation of direct-to-consumer advertising or efforts at the border to prevent the importation of prescription or counterfeit pharmaceutical products; and
- the Special Access Program or Patented Medicines Prices Review Board.

Criteria

To determine whether Health Canada fulfilled its key responsibilities for the timeliness and consistency of clinical trial application reviews, we used the following criteria:	
Criteria	**Sources**
Health Canada reviews clinical trial applications in a timely fashion.	• Guidance for Industry: Management of Drug Submissions, Health Canada • *Food and Drug Regulations*
To determine whether the Department fulfilled its key responsibilities for supporting the transparency of authorized clinical trials and for verifying their regulatory compliance, we used the following criteria:	
Criteria	**Sources**
The Department publicly discloses information related to clinical trials that are in progress, abandoned, or completed.	• Blueprint for Renewal II: Modernizing Canada's Regulatory System for Health Products and Food, Health Canada • Health Products and Food Branch Strategic Plan, Health Canada, 2007–2012 • Opening the Medicine Cabinet: First Report on Health Aspects of Prescription Drugs by the House of Commons Standing Committee on Health

The Department uses a risk-based approach to inspect clinical trial sites and to monitor adverse drug reactions in order to verify compliance with the *Food and Drug Regulations*.	• Framework for the Management of Risk, Treasury Board • Decision-Making Framework for Identifying, Assessing and Managing Health Risks, Health Canada • Health Product and Food Branch's Compliance and Enforcement Risk Evaluation Guide: An Approach to Decision-Making, Health Canada • *Food and Drug Regulations*
To determine whether Health Canada fulfilled its key responsibilities for conducting timely and consistent submission reviews, for supporting the transparency of review outcomes and for implementing systems to manage conflicts of interest, we used the following criteria:	
Criteria	**Sources**
The Department reviews pharmaceutical submissions in a timely manner.	• *User Fees Act* • Guidance for Industry: Management of Drug Submissions, Health Canada
The Department establishes quality assurance systems to support the consistent review of pharmaceutical submissions	• Health Products and Food Branch Strategic Plan, Health Canada, 2007–2012 • Therapeutic Products Directorate Strategic Plan 2006–2009, Health Canada • ISO9001:2008
The Department publicly discloses information related to its review of pharmaceutical submissions that have been approved, rejected, or withdrawn	• Cabinet Directive on Streamlining, Our Commitment to Canadians • Health Products and Food Branch Strategic Plan, Health Canada, 2007–2012
The Department implements systems to manage risks to the review process arising from real, apparent, or potential conflicts of interest	• Values and Ethics Code for the Public Service, Treasury Board • Health Products and Food Branch Strategic Plan, Health Canada, 2007–2012
To determine whether Health Canada fulfilled its key responsibilities for monitoring the safety of marketed pharmaceuticals, for communicating safety concerns in a timely manner, and for verifying the regulatory compliance of the pharmaceutical industry, we used the following criteria:	
Criteria	**Sources**
The Department uses a risk-based approach to monitor the safety of pharmaceuticals authorized for use in Canada	• Federal Regulatory Post-Market Surveillance Strategy, Health Canada • Therapeutic Access Strategy, Health Canada
The Department uses a risk-based approach to enforce industry's compliance with the sections of the *Food and Drug Regulations* pertaining to pharmaceuticals	• Framework for the Management of Risk, Treasury Board • Decision-Making Framework for Identifying, Assessing and Managing Health Risks, Health Canada • Health Product and Food Branch's Compliance and Enforcement Risk Evaluation Guide: An Approach to Decision-Making, Health Canada • *Food and Drug Regulations*
The Department communicates safety risks to health care professionals and the public in a timely manner and assessed the effectiveness of its communications	• Federal Regulatory Post-Market Surveillance Strategy, Health Canada • Description of Current Risk Communication Documents for Marketed Health Products for Human Use, Health Canada

Management reviewed and accepted the suitability of the criteria used in the audit.

Period covered by the audit

The period under audit was 1 January 2009 to 31 December 2010. Audit work for this chapter was substantially completed on 31 May 2011.

Audit team

Assistant Auditor General: Neil Maxwell
Principal: Louise Dubé
Lead Auditor: Mark Carroll

Irene Andayo
Daphné Lamontagne
Margaretha Ysselstein

For information, please contact Communications at 613-995-3708 or 1-888-761-5953 (toll-free).

Appendix List of recommendations

The following is a list of recommendations found in Chapter 4. The number in front of the recommendation indicates the paragraph where it appears in the chapter. The numbers in parentheses indicate the paragraphs where the topic is discussed.

Recommendation	Response
Regulating clinical trials	
4.35 Health Canada should strengthen its risk-based approach for monitoring and assessing clinical trial adverse drug reaction reports and for inspecting clinical trial sites, so potential safety issues are mitigated. **(4.16–4.34)**	Agreed. The Department is strengthening its risk-based approach to monitor and assess clinical trial adverse drug reaction reports and clinical trial inspections. A detailed standard operating procedure and strategy guide has been developed to prioritize the review of individual adverse drug reaction reports. This approach was implemented on 4 July 2011. The Department expects to have completed a review of the existing risk-based process for selecting clinical trial inspection sites by fall 2011. This review will be used to assess the effectiveness of the existing process and to inform the development, documentation, and implementation of an enhanced process.
4.36 Health Canada should establish timelines for officially notifying clinical trial sites of non-compliant ratings and for reviewing proposed corrective measures to verify compliance with the *Food and Drug Regulations*. **(4.16–4.34)**	Agreed. The Department is currently reviewing and revising its existing standard operating procedure for conducting clinical trial inspections. This revised standard operating procedure will emphasize establishing timelines for key steps in the inspection process, including notification of non-compliant ratings and the review of proposed corrective measures. This work will be completed by 31 March 2013.
4.41 Health Canada should fulfill long-standing commitments to enhance public access to information on authorized clinical trials, including the results of its clinical trial inspections. **(4.37–4.40)**	Agreed. The Department will develop policies on enhancing public access to information on authorized clinical trials that respect privacy rights and legislation. Work began in 2011 and will be completed by 31 March 2013. The Department commits to publishing periodic reports regarding clinical trial inspections, to provide stakeholders and the public with a summary view of its inspection findings by 31 March 2012.

Recommendation	Response
Reviewing drug submissions	
4.53 Health Canada should ensure that it meets service standards for the review of all drug submission types—by giving due consideration to the appropriate allocation of additional resources from increased fees charged to industry, to the use of foreign regulatory information, and to streamlining its review processes. **(4.45–4.52)**	Agreed. Revenues from recently updated user fees will allow the Department to meet its well-established and internationally recognized performance standards. The Department will closely monitor its performance. It will continue to seek process efficiencies, such as increasing the leverage of external scientific expertise and the use of foreign regulatory information. The Department will begin piloting an approach to enhance and formalize the use of foreign reviews through standard operating procedures and guidance for industry in the fall of 2011 and will complete an evaluation of the pilot by 31 March 2014.
4.57 Health Canada should regularly assess whether the procedures and guidelines, which were established to ensure timely, consistent, and high-quality review decisions, are interpreted and applied consistently by all four review bureaus. **(4.54–4.56)**	Agreed. The Department will develop a system to regularly assess and ensure the use of procedures established to ensure timely, consistent, and high-quality review decisions by 31 December 2012. Implementation of the system, which will include assessment of compliance with procedures and consistency of interpretation across organization review units, and necessary corrective mechanisms to ensure consistent use, will be completed by 31 December 2013.
4.63 Health Canada should disclose information related to new drug approvals in a timely manner and improve the transparency of "approvals with conditions," rejections, and withdrawals of new drugs so that Canadians and health care professionals can access information about these drugs. **(4.58–4.62)**	Agreed. The Department will improve the transparency of approvals with conditions, rejections, and withdrawals to the Canadian public. The Department will consult with stakeholders in fall 2011 about expanding its public communications on post-approval decisions for marketed health products to include information on approvals with conditions, rejections, and withdrawals, with a view to disclosing additional information by June 2012.
4.70 Health Canada should assess the risks posed by conflicts of interest to the drug review process, determine what measures are necessary to manage these risks, and implement those measures. **(4.64–4.69)**	Agreed. The Department requires disclosure of potential conflicts of interest at the initiation of employment, and employees are subject to the Values and Ethics Code for the Public Service. The Department will determine if there are any particular risks posed by potential conflicts of interest in the drug review process by 31 March 2012 and, if necessary, develop and implement additional measures by 30 September 2012.

Recommendation	Response
Monitoring post-market safety	
4.96 Health Canada should improve the timeliness of safety assessments and the implementation of related recommendations to update labels and to issue risk communications, so Canadians and health care professionals can be informed of new drug safety information in a timely manner. **(4.73–4.95)**	Agreed. The Department will improve the timeliness of safety assessments by fully implementing and respecting related performance standards by December 2013. This involves reviewing baselines for completing safety reviews.
4.97 Health Canada should establish a systematic process to manage safety assessment recommendations for marketed drugs, to ensure that recommendations are dealt with appropriately and in a timely manner. **(4.79–4.95)**	Agreed. The Department will establish a systematic process to implement safety assessment recommendations for marketed drugs. The Department has already begun developing a standard operating procedure in this regard. The standard operating procedure will include new formalized tracking systems (currently under development) and necessary implementation procedures following a safety assessment recommendation. This will be in place by 31 March 2013.
Enforcing compliance with the regulations	
4.109 Health Canada should consistently apply its risk-based standard operating procedures, so the priority of the drug complaints it receives is properly documented and addressed in a timely manner. **(4.100–4.108)**	Agreed. The Department strives to ensure that complaints received are addressed in a timely manner and are properly documented. The Department will review its processes to ensure better documentation, conduct training sessions, and implement more robust performance monitoring by 31 March 2013.

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